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Drafts  
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Active  
L1: (46084) (recombinant adeno-associated virus) or (rAAV)  
L3: (558146) gene transfer or gene therapy  
L5: (35955) L1 and L3  
L7: (3934) L5 and cardio\$  
L11: (1272) 17 AND (perfus\$ near3 coronary artery)  
L13: (196) 17 AND (perfus\$ near3 coronary sinus)  
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Patent Examiner's Toolkit

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NEWS 4	Oct 27	SET ABBREVIATIONS and SET PLURALS extended in Derwent World Patents Index files
NEWS 5	Oct 27	Patent Assignee Code Dictionary now available in Derwent Patent Files
NEWS 6	Oct 27	Plasdoc Key Serials Dictionary and Echoing added to Derwent Subscriber Files WPIDS and WPIX
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=> s ((RAAV) or (recombinant adeno associated vir?))

5 FILES SEARCHED...

L1 2108 ((RAAV) OR (RECOMBINANT ADENO ASSOCIATED VIR?))

=> L1 and (gene thaerapy or gene transfer)

L1 IS NOT A RECOGNIZED COMMAND

The previous command name entered was not recognized by the system.  
For a list of commands available to you in the current file, enter  
"HELP COMMANDS" at an arrow prompt (=>).

=> s L1 and (gene thaerapy or gene transfer)

2 FILES SEARCHED...

L2 1003 L1 AND (GENE THAERAPY OR GENE TRANSFER)

=> s L1 and (gene therapy or gene transfer)

2 FILES SEARCHED...

6 FILES SEARCHED...

L3 1649 L1 AND (GENE THERAPY OR GENE TRANSFER)

=> L3 and cardio?

L3 IS NOT A RECOGNIZED COMMAND

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"HELP COMMANDS" at an arrow prompt (=>).

=> s l3 and cardio?

L4 31 L3 AND CARDIO?

=> d his

FILE 'DGENE, CAPLUS, BIOSIS, MEDLINE, BIOTECHDS, ASE, SCISEARCH'  
ENTERED AT 11:47:28 ON 12 FEB 2001

L1 2108 S ((RAAV) OR (RECOMBINANT ADENO ASSOCIATED VIR?))  
L2 1003 S L1 AND (GENE THERAPY OR GENE TRANSFER)  
L3 1649 S L1 AND (GENE THERAPY OR GENE TRANSFER)  
L4 31 S L3 AND CARDIO?

=> dup rem 14

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PROCESSING COMPLETED FOR L4

L5 23 DUP REM L4 (8 DUPLICATES REMOVED)

=> d ibib abs 15 1-23

L5 ANSWER 1 OF 23 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:456818 CAPLUS

DOCUMENT NUMBER: 133:53712

TITLE: Efficient and stable in vivo **gene transfer to cardiomyocytes** using **recombinant adeno-associated virus** vectors

INVENTOR(S): Leiden, Jeffrey M.; Svensson, Eric

PATENT ASSIGNEE(S): Arch Development Corp., USA

SOURCE: PCT Int. Appl., 20 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000038518	A1	20000706	WO 1999-US31093	19991228
W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			

PRIORITY APPLN. INFO.: US 1998-113923 19981228

AB **Recombinant adeno-assocd. virus** (**rAAV**) vectors are used to transduce **cardiomyocytes** in vivo by infusing the **rAAV** into a coronary artery or coronary sinus. **RAAV** infection is not assocd. with detectable myocardial inflammation or myocyte necrosis. Thus, **rAAV** is a useful vector for the stable expression of therapeutic genes in the myocardium and can be used to deliver genes for inducing angiogenesis, inhibiting angiogenesis, stimulating cell proliferation, inhibiting cell proliferation and/or treating or ameliorating other **cardiovascular** conditions.

REFERENCE COUNT: 4

REFERENCE(S): (1) Alexander; Clinical and Experimental Pharmacology and Physiology 1999, V26(9), P661 CAPLUS  
(2) Gnatenko; Journal of Investigative Medicine 1997, V45(2), P87 MEDLINE  
(3) Kaplitt; Annals of Thoracic Surgery 1996, V62(6), P1669 MEDLINE  
(4) Svensson; Circulation 1999, V99(2), P201 MEDLINE

L5 ANSWER 2 OF 23 CAPLUS COPYRIGHT 2001 ACS  
ACCESSION NUMBER: 2000:839304 CAPLUS  
DOCUMENT NUMBER: 133:345555

TITLE: A novel **recombinant adeno-associated virus** vector packaging system with HSV-1 amplicon providing helper functions  
INVENTOR(S): Wu, Xiaobing; Wu, Zhijiang; Hou, Yunde  
PATENT ASSIGNEE(S): National Major Laboratory of Virus & Gene Engineering,  
Peop. Rep. China  
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 8 pp.  
CODEN: CNXXEV  
DOCUMENT TYPE: Patent  
LANGUAGE: Chinese  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1252441	A	20000510	CN 1999-119039	19990910

AB A novel packaging system for producing **recombinant adeno-associated virus (rAAV)** vector is described. Instead of the conventional method for **rAAV** prodn. by two-plasmid co-transfection followed by superinfection with adenovirus 5, a strategy of "one host cell line/one helper virus" is designed. An HSV-1 amplicon system expressing AAV-2 rep and cap genes from their native promoters was used to provide complete helper functions for **rAAV** replicating and packaging. This HSV-1 amplicon stock consisted of two kinds of infectious HSV-1 virions, a replicating-defective HSV-1 amplicon pseudovirus harboring multi-copies of AAV-2 rep and cap gene and a temp.-sensitive HSV-1 mutant strain ts-KOS. The process comprises prepg. **rAAV** packaging cell line; inserting AAV rep/cap gene into herpes simplex virus-I or(-II) at UL2 and/or UL44 gene to generate full functional helper virus; infecting **rAAV** packaging cells with HSV-1 helper virus for prepg. and screening for **rAAV** virus. The **rAAV** packaging cell contains AAV ITRs and therapeutic gene fragment. The **rAAV** packaging cell can be selected from BHK cell, KB cell, 293 cell, and HeLa cell. The **rAAV** vector contains antibiotic-resistance gene such as neo gene or hph gene. High-titer **rAAV** was generated with this new packaging system. This packaging system gives a simple and scaleable process for **rAAV** prodn. which can be used for gene delivery in **gene therapy**.

L5 ANSWER 3 OF 23 BIOSIS COPYRIGHT 2001 BIOSIS  
ACCESSION NUMBER: 2000:312313 BIOSIS  
DOCUMENT NUMBER: PREV200000312313  
TITLE: Gene delivery to in situ veins: Differential effects of adenovirus and adeno-associated viral vectors.  
AUTHOR(S): Eslami, Mohammad H.; Gangadharan, Sidhu P.; Sui, XinXin; Rhynhart, Kurt K.; Snyder, Richard O.; Conte, Michael S.  
SOURCE: Journal of Vascular Surgery, (June, 2000) Vol. 31, No. 6, pp. 1149-1159. print.  
ISSN: 0741-5214.  
DOCUMENT TYPE: Article  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
AB Purpose: **Gene transfer** offers the potential to modify vein graft biology at the time of surgical implantation. Efficiency of gene delivery, stability of expression, and host responses are critical parameters for candidate vectors. We compared the effects of intra-luminal exposure with adenovirus (AD) and adeno-associated virus (AAV) vectors on transgene expression and monocyte adhesion (MA) in treated vein segments.

Methods: Adult New Zealand white rabbits (N = 51) were anesthetized, and the jugular veins were cannulated bilaterally. Veins were gently distended with either vector (2.108 to 1.1010 infective particles/mL) or vehicle (control) for 30 minutes, after which venous flow was restored. AD and AAV vectors encoding for the marker genes beta-galactosidase (LacZ) and green fluorescent protein (GFP) were used. Vessels were explanted 2 to 40 days postinfection for analysis of gene expression (X-gal staining, reverse transcriptase-polymerase chain reaction), MA, and immunohistochemistry. Ex vivo adhesion assays used 51Cr-labeled THP-1 cells. Statistical significance was tested by using analysis of variance with a P value less than .05. Results: All animals survived, and all treated veins were patent at sacrifice. Intraluminal exposure to AD at a titer of 1.109 resulted in near complete transduction of the endothelium at 2 days, with no detectable expression by day 14. At an equal titer of infectious particles, transgene expression was markedly less for AAV at 2 to 7 days, but improved at 2 weeks and persisted to 40 days. MA was significantly increased 2 days after AD exposure (2.7-fold vs control, \*P < .002); AAV treatment had no discernible effect on MA. Conclusion: AD-mediated **gene transfer** to vein segments resulted in robust, transient gene expression that disappeared after 2 weeks. In comparison, AAV-mediated gene delivery was less efficient, but resulted in delayed onset, persistent expression beyond 30 days. AD exposure induced an early increase in MA to the vein surface that was not seen with AAV treatment. Current generations of both AD and AAV vectors have significant, albeit different, limitations for vascular **gene therapy**.

L5 ANSWER 4 OF 23 BIOSIS COPYRIGHT 2001 BIOSIS  
ACCESSION NUMBER: 2000:523433 BIOSIS  
DOCUMENT NUMBER: PREV200000523433  
TITLE: **Gene therapy for hypertension:  
Recombinant adeno-associated  
virus** vector delivery of angiotensin type 1  
receptor antisense in hypertensive double transgenic  
mice.  
AUTHOR(S): Phillips, M. Ian (1); Kimura, Birgitta (1); Zhang, Y.  
Clare (1); Gelband, Craig H. (1); Sigmund, Curt D.; Mohuczy,  
Dagmara  
CORPORATE SOURCE: (1) Univ of Florida, Gainesville, FL USA  
SOURCE: Hypertension (Baltimore), (October, 2000) Vol. 36, No. 4,  
pp. 730. print.  
Meeting Info.: 54th Annual Fall Conference and Scientific  
Sessions of the Council for High Blood Pressure Research  
Washington, DC, USA November 24-27, 2000  
ISSN: 0194-911X.  
DOCUMENT TYPE: Conference  
LANGUAGE: English  
SUMMARY LANGUAGE: English

L5 ANSWER 5 OF 23 BIOSIS COPYRIGHT 2001 BIOSIS  
ACCESSION NUMBER: 2000:523428 BIOSIS  
DOCUMENT NUMBER: PREV200000523428  
TITLE: Attenuation of hypertension and heart hypertrophy by  
**recombinant adeno-associated  
virus** delivering angiotensinogen antisense (  
**rAAV-AGT-AS**).  
AUTHOR(S): Kimura, Birgitta (1); Mohuczy, Dagmara (1); Tang, Xiaoping  
(1); Phillips, M. Ian (1)  
CORPORATE SOURCE: (1) Univ of Florida, Gainesville, FL USA  
SOURCE: Hypertension (Baltimore), (October, 2000) Vol. 36, No. 4,  
pp. 729. print.  
Meeting Info.: 54th Annual Fall Conference and Scientific

DOCUMENT TYPE:  
LANGUAGE:  
SUMMARY LANGUAGE:

Conference  
English  
English

L5 ANSWER 6 OF 23 BIOSIS COPYRIGHT 2001 BIOSIS  
ACCESSION NUMBER: 2000:488112 BIOSIS  
DOCUMENT NUMBER: PREV200000488233

TITLE: **Gene therapy** vectors based on  
adeno-associated virus: Characteristics and applications  
to

AUTHOR(S): Athanasopoulos, Takis; Fabb, Stewart; Dickson, George (1)  
CORPORATE SOURCE: (1) University Chair of Molecular Cell Biology, School of  
Biological Sciences, Division of Biochemistry, Royal  
Holloway College, University of London, Egham Hill, Egham,  
Surrey, TW20 0EX UK

SOURCE: International Journal of Molecular Medicine, (October,  
2000) Vol. 6, No. 4, pp. 363-375. print.  
ISSN: 1107-3756.

DOCUMENT TYPE: General Review  
LANGUAGE: English  
SUMMARY LANGUAGE: English

AB Adeno-associated virus (AAV), a defective parvovirus, was discovered more  
than 30 years ago. Interest in this virus for human **gene  
therapy** applications focuses on its non-pathogenicity, broad  
tropism and infectivity, site-specific integration and long-term  
persistence. The field of **rAAV** research has considerably  
advanced: titers of 10<sup>14</sup> p/ml have been achieved, plasmid systems devised  
to produce helper-free viruses, chimaeric vectors combining properties of  
**rAAV** ITRs and large sequence capacity from Ad/HS vectors in  
parallel with the revolutionary intron strategy based on  
heterodimerisation of the forming concatamers have expanded the vector  
capacity. Muscle cells and neurons (post-mitotic cells) are amongst the  
most efficient targets of **rAAV** delivery and AAV receptors and  
co-receptors have been identified. This review will describe advances in  
the field of **rAAV** technology that overcome certain limitations  
of the vector as a gene delivery system and overview applications  
involving these recombinant vectors for the treatment of acquired and  
inherited diseases.

L5 ANSWER 7 OF 23 SCISEARCH COPYRIGHT 2001 ISI (R)  
ACCESSION NUMBER: 2000:872601 SCISEARCH  
THE GENUINE ARTICLE: 351BR  
TITLE:

Morphological and physiological rescue of dilated  
**cardiomyopathy** (DCM) by **rAAV**  
vector-mediated **gene transfer** in vivo

AUTHOR: Kawada T (Reprint); Nakazawa M; Sakamoto A; Urabe M; Wang  
Y; Ozawa K; Toyooka T

CORPORATE SOURCE: NIIGATA UNIV, HOSP MED, DIV PHARM, NIIGATA, JAPAN;  
NIIGATA

UNIV, SCH MED, DEPT PHARMACOL, NIIGATA 951, JAPAN; NATL  
CARDIOVASC RES CTR, DIV BIOTECHNOL, OSAKA, JAPAN; JICHI  
MED SCH, DIV GENET THERAPEUT, TOCHIGI, JAPAN; UNIV TOKYO,  
DEPT INTERNAL MED, TOKYO, JAPAN

COUNTRY OF AUTHOR: JAPAN

SOURCE: EUROPEAN HEART JOURNAL, (AUG-SEP 2000) Vol. 21, Supp.  
[S],

pp. 132-132.

Publisher: W B SAUNDERS CO LTD, 24-28 OVAL RD, LONDON NW1  
7DX, ENGLAND.

ISSN: 0195-668X.

DOCUMENT TYPE: Conference; Journal  
FILE SEGMENT: CLIN

LANGUAGE: English  
REFERENCE COUNT: 0

L5 ANSWER 8 OF 23 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 2001:35379 BIOSIS

DOCUMENT NUMBER: PREV200100035379

TITLE: Rescue of DCM by **gene therapy**: A novel and general scheme for advancing heart failure and its protection.

AUTHOR(S): Toyo-Oka, T. (1); Kawada, T.; Nakazawa, M.; Sakamoto, A.; Urabe, M.; Masui, F.; Yoshida, H.; Nakauchi, S.; Xi, H.; Shin, W. S.; Sato, H.; Monahan, J.; Takeo, S.; Ozawa, K.

CORPORATE SOURCE: (1) Dept. Cardiovasc. Med., Univ. Tokyo, Tokyo Japan  
SOURCE: Journal of Molecular and Cellular Cardiology, (November, 2000) Vol. 32, No. 11, pp. A88. print.  
Meeting Info.: XVII Annual Meeting of the International Society for Heart Research, Japanese Section Osaka, Japan December 06-08, 2000 International Society for Heart Research  
. ISSN: 0022-2828.

DOCUMENT TYPE: Conference

LANGUAGE: English

SUMMARY LANGUAGE: English

L5 ANSWER 9 OF 23 SCISEARCH COPYRIGHT 2001 ISI (R)

ACCESSION NUMBER: 2001:53243 SCISEARCH

THE GENUINE ARTICLE: 367QE

TITLE: Dilated **cardiomyopathy** (DCM) is rescued by **recombinant adeno-associated virus (rAAV)**-mediated somatic **gene therapy**

AUTHOR: Toyo-Oka T (Reprint); Kawada T; Nakazawa M; Sakamoto A;

CORPORATE SOURCE: Urabe M; Wang Y; Shin W S; Sato H; Monahan J; Ozawa K  
Univ Tokyo, Tokyo, Japan; Niigata Univ, Hosp Med, Div Pharma, Niigata, Japan; Niigata Univ, Niigata, Japan; NCVRC, Biotech Div, Osaka, Japan; Jichi Med Sch, Tochigi, Japan; Univ Tokyo, Tokyo, Japan; Avigen Inc, Alameda, CA USA

COUNTRY OF AUTHOR: Japan; USA

SOURCE: CIRCULATION, (31 OCT 2000) Vol. 102, No. 18, Supp. [S], pp. 11-11. MA 42.  
Publisher: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA.  
ISSN: 0009-7322.

DOCUMENT TYPE: Conference; Journal

LANGUAGE: English

REFERENCE COUNT: 0

L5 ANSWER 10 OF 23 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 2000:481338 BIOSIS

DOCUMENT NUMBER: PREV200000481338

TITLE: Morphological and physiological rescue of dilated **cardiomyopathy** (DCM) by **rAAV** vector-mediated **gene transfer** in vivo.

AUTHOR(S): Kawada, T. (1); Nakazawa, M.; Sakamoto, A.; Urabe, M.; Wang, Y.; Ozawa, K.; Toyo-Oka, T.

CORPORATE SOURCE: (1) Div. of Pharmacy, Niigata Univ. Medical Hospital, Niigata Univ. School of Medicine, Niigata Japan

SOURCE: European Heart Journal, (August September, 2000) Vol. 21, No. Abstract Supplement, pp. 3. print.  
Meeting Info.: XXII Congress of the European Society of Cardiology Amsterdam, Netherlands August 26-30, 2000 European Society of Cardiology  
. ISSN: 0195-668X.

DOCUMENT TYPE: Conference

LANGUAGE: English



L5 ANSWER 11 OF 23 BIOSIS COPYRIGHT 2001 BIOSIS  
 ACCESSION NUMBER: 2001:68588 BIOSIS  
 DOCUMENT NUMBER: PREV200100068588

TITLE: Dilated **cardiomyopathy** (DCM) is rescued by  
**recombinant adeno-associated**  
**virus (rAAV)-mediated somatic**  
**gene therapy.**

AUTHOR(S): Toyo-Oka, Teruhiko (1); Kawada, Tomie; Nakazawa, Mikio;  
 Sakamoto, Aiji; Urabe, Masashi; Wang, Yue; Shin, Wee Soo;  
 Sato, Hiroshi; Monahan, John; Ozawa, Keiya  
 CORPORATE SOURCE: (1) Univ of Tokyo, Tokyo Japan  
 SOURCE: Circulation, (October 31, 2000) Vol. 102, No. 18  
 Supplement, pp. II.11. print.  
 Meeting Info.: Abstracts from Scientific Sessions 2000 New  
 Orleans, Louisiana, USA November 12-15, 2000  
 ISSN: 0009-7322.  
 DOCUMENT TYPE: Conference  
 LANGUAGE: English  
 SUMMARY LANGUAGE: English

L5 ANSWER 12 OF 23 CAPLUS COPYRIGHT 2001 ACS  
 ACCESSION NUMBER: 1999:635437 CAPLUS  
 DOCUMENT NUMBER: 131:253345

TITLE: Adeno-associated virus vectors for **gene**  
**therapy** of muscle disease  
 INVENTOR(S): Podsakoff, Gregory M.; Kessler, Paul D.; Byrne, Barry  
 J.; Kurtzman, Gary J.  
 PATENT ASSIGNEE(S): Avigen, Inc., USA; Johns Hopkins University  
 SOURCE: U.S., 27 pp., Cont.-in-part of U.S. Ser. No. 588,355.  
 CODEN: USXXAM  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 4  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5962313	A	19991005	US 1997-784757	19970116
US 5858351	A	19990112	US 1996-588355	19960118
WO 9726337	A1	19970724	WO 1997-US895	19970117
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT,				
CA 2243261	AA	19970724	CA 1997-2243261	19970117
EP 874904	A1	19981104	EP 1997-904823	19970117
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				
IE, FI				
PRIORITY APPLN. INFO.:			US 1996-588355	19960118
			US 1997-784757	19970116
			WO 1997-US895	19970117

AB The use of **recombinant adeno-assocd.**  
**virus** (AAV) virions for delivery of therapeutic genes to muscle is  
 disclosed. The invention allows for the direct, in vivo injection of  
 recombinant AAV virions into muscle tissue, as well as for the in vitro  
 transduction of muscle cells that can subsequently be introduced into a  
 subject for treatment. The invention provides for sustained, high-level  
 expression of the delivered gene and for in vivo secretion of the  
 therapeutic protein from transduced muscle cells such that systemic  
 delivery is achieved. Adeno-assocd. virus can transform myocytes and  
**cardiomyocytes** with a lacZ reporter gene in vitro. Transformation  
 of mouse myotubes and myoblasts with a virus carrying the human  
 erythropoietin gene led to the synthesis of the protein by transformed  
 cells for 6-8 wk. I.m. injection was mor effective at transformation of  
 muscle cells and tissues than was i.v. injection. Use of an AAV vector  
 to

of cellliveran acid .alpha.-glucosidase gene that could be used for therapy

**cardiomyopathy** associated with glycogen storage disease is described. Mice inoculated i.m. with the virus produced elevated levels of the enzyme for 10 wk.

REFERENCE COUNT: 30

REFERENCE(S): (2) Acsadi; Hum Mol Genetics 1994, V3, P579 CAPLUS  
(3) Acsadi; Nature 1991, V352, P815 CAPLUS  
(4) Anon; WO 9413788 1994 CAPLUS  
(5) Anon; WO 9513376 1995 CAPLUS  
(6) Anon; WO 9520671 1995 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 13 OF 23 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 1

ACCESSION NUMBER: 1999:257740 CAPLUS

DOCUMENT NUMBER: 131:53931

TITLE: Stable restoration of the sarcoglycan complex in dystrophic muscle perfused with histamine and a **recombinant adeno-associated viral vector**

AUTHOR(S): Greelish, James P.; Su, Leonard T.; Lankford, Edward B.; Burkman, James M.; Chen, Haiyan; Konig, Stephane K.; Mercier, Isabelle M.; Desjardins, Philippe R.; Mitchell, Marilyn A.; Zheng, Xiang Guang; Leferovich, John; Ping, Guang Gao; Balice-Gordon, Rita J.; Wilson,

CORPORATE SOURCE: James M.; Stedman, Hansell H. Departments of Surgery, Medicine, Neuroscience3 and Molecular and Cellular Engineering and Institute for Human Gene Therapy, University of Pennsylvania Health System, Philadelphia, PA, 19104, USA

SOURCE: Nat. Med. (N. Y.) (1999), 5(4), 439-443

CODEN: NAMEFI; ISSN: 1078-8956

PUBLISHER: Nature America

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Limb-girdle muscular dystrophies 2C-F represent a family of autosomal recessive diseases caused by defects in sarcoglycan genes. The **cardiomyopathic** hamster is a naturally occurring model for limb-girdle muscular dystrophy caused by a primary deficiency in .delta.-sarcoglycan. We show here that acute sarcolemmal disruption occurs in this animal model during forceful muscle contraction. A **recombinant adeno-associated virus** vector encoding human .delta.-sarcoglycan conferred efficient and stable genetic reconstitution in the adult **cardiomyopathic** hamster when injected directly into muscle. A quant. assay demonstrated that vector-transduced muscle fibers are stably protected from sarcolemmal disruption; there was no associated inflammation or immunol. response to the vector-encoded protein. Efficient gene transduction with rescue of the sarcoglycan complex in muscle fibers of the distal hindlimb was also obtained after infusion of **recombinant adeno-associated virus** into the femoral artery in conjunction with histamine-induced endothelial permeabilization. This study provides a strong rationale for the development of **gene therapy** for limb-girdle muscular dystrophy.

REFERENCE COUNT: 21

REFERENCE(S): (3) Cox, G; Nature 1993, V364, P725 CAPLUS  
(4) Cox, G; Nature Genet 1994, V8, P333 CAPLUS  
(5) DeMatteo, R; J Virol 1997, V71, P5330 CAPLUS  
(6) Deconinck, N; Proc Natl Acad Sci USA 1996, V93, P3570 CAPLUS  
(7) Fisher, K; Nature Med 1997, V3, P306 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 14 OF 23 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 1999:123147 BIOSIS

DOCUMENT NUMBER: PREV199900123147  
 TITLE: Antisense inhibition of AT1 receptors in vascular smooth muscle cells using adeno-associated virus-based vector.  
 AUTHOR(S): Monuczny, Dagmara; Gelband, Craig H.; Phillips, M. Ian (1)  
 CORPORATE SOURCE: (1) Dep. Physiol., Coll. Med., Univ. Fla., Box 100274, Gainesville, FL 32610 USA  
 SOURCE: Hypertension (Baltimore), (Jan., 1999) Vol. 33, No. 1 PART 2, pp. 354-359.  
 ISSN: 0194-911X.  
 DOCUMENT TYPE: Article  
 LANGUAGE: English

AB Vascular smooth muscle cells (VSMCs) are the main peripheral target for vasoconstriction and growth-promoting activity of angiotensin II (Ang II), acting through angiotensin type I receptors (AT1-R). Current antihypertension treatments include daily reductions in the effects of Ang II. To decrease an effect of Ang II in a prolonged fashion, we have developed an adeno-associated virus (AAV) vector with antisense DNA for AT1-R. AAV has many advantages over other viral vectors. AAV is nonpathogenic, does not stimulate inflammation or immune reaction and enters nondividing cells, and provides stable long-term gene expression. To test AAV in VSMCs, we constructed and tested plasmid AAV (pAAV) and recombinant AAV (rAAV) with AT1-R antisense DNA. **rAAV** was constructed with a cassette containing a cytomegalovirus promoter and the cDNA for the AT1-R inserted in the antisense direction. The cassette was packaged into the virion. Transfection of VSMCs with the pAAV antisense to AT1-R produced a significant reduction in the amount of AT1-R (P<0.01). Transduction of VSMCs with the **rAAV-AT1-R-AS** at MOI of 5 also showed significant reduction of AT1-R and long-lasting expression of the transgene for at least 8 weeks. The reduction of AT1-R number in VSMCs was concomitant with a decrease in the Ang II-stimulated increase of intracellular calcium. The results show that AAV vector delivers AT1-R antisense to inhibit AT1-R in VSMCs. For the purpose of **gene therapy** for hypertension, it is necessary to demonstrate the effectiveness of a vector system in VSMCs. This study provides support for the potential use of AAV AT1-R antisense in VSMCs.

L5 ANSWER 15 OF 23 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 2  
 ACCESSION NUMBER: 1999:86561 BIOSIS  
 DOCUMENT NUMBER: PREV199900086561  
 TITLE: Efficient and stable transduction of **cardiomyocytes** after intramyocardial injection or intracoronary perfusion with **recombinant adeno-associated virus** vectors.

AUTHOR(S): Svensson, Eric C.; Marshall, Deborah J.; Woodard, Karen; Lin, Hua; Jiang, Fang; Chu, Lein; Leiden, Jeffrey M. (1)  
 CORPORATE SOURCE: (1) Univ. Chicago, Room B608 MC 6080, 5841 S. Maryland Ave., Chicago, IL 60637 USA  
 SOURCE: Circulation, (Jan. 19, 1999) Vol. 99, No. 2, pp. 201-205.  
 ISSN: 0009-7322.  
 DOCUMENT TYPE: Article  
 LANGUAGE: English

AB Background-The delivery of recombinant genes to **cardiomyocytes** holds promise for the treatment of a variety of **cardiovascular** diseases. Previous **gene transfer** approaches that used direct injection of plasmid DNA or replication-defective adenovirus vectors have been limited by low transduction frequencies and transient transgene expression due to immune responses, respectively. In this report, we have tested the feasibility of using intramyocardial injection or intracoronary infusions of **recombinant adeno-associated virus (rAAV)** vectors to program transgene expression in murine **cardiomyocytes** in vivo. Methods

and Results-We constructed an **rAAV** containing the LacZ gene under the transcriptional control of the cytomegalovirus (CMV) promoter (AAVCMV-LacZ). We then injected  $1 \times 10^8$  infectious units (IU) of this virus into the left ventricular myocardium of adult CD-1 mice. Control hearts were injected with the AdCMV-LacZ adenovirus vector. Hearts harvested 2, 4, and 8 weeks after AAVCMV-LacZ injection demonstrated stable beta-galactosidase (beta-gal) expression in large numbers of **cardiomyocytes** without evidence of myocardial inflammation or myocyte necrosis. In contrast, the AdCMV-LacZ-injected hearts displayed transient beta-gal expression, which was undetectable by 4 weeks after injection. Explanted C57BL/6 mouse hearts were also perfused via the coronary arteries with  $1.5 \times 10^9$  IU of AAVCMV-LacZ and assayed 2, 4, and

8

weeks later for beta-gal expression. beta-Gal expression was detected in <1% of **cardiomyocytes** at 2 weeks after perfusion but was detected in up to 50% of **cardiomyocytes** 4 to 8 weeks after perfusion. Conclusions-Direct intramyocardial injection or coronary artery

perfusion with **rAAV** vectors can be used to program stable transgene expression in **cardiomyocytes** in vivo. **rAAV** appears to represent a useful vector for the delivery of therapeutic genes to the myocardium.

L5 ANSWER 16 OF 23 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 1998:524127 BIOSIS

DOCUMENT NUMBER: PREV199800524127

TITLE: **Recombinant adeno-associated virus-mediated gene transfer in the in vivo rabbit myocardium.**

AUTHOR(S): Wright, M. J. (1); De Alwis, M.; Latchman, D. S.; Thrasher,

A. J.; Marber, M. S. (1)

CORPORATE SOURCE: (1) Dep. Cardiol., Rayne Inst., United Med. Dent. Sch., St.

Thomas' Hosp., London UK

SOURCE: European Heart Journal, (Aug., 1998) Vol. 19, No. ABST. SUPPL., pp. 478.

Meeting Info.: XXth Congress of the European Society of Cardiology Vienna, Austria August 22-26, 1998 European Society of Cardiology . ISSN: 0195-668X.

DOCUMENT TYPE: Conference

LANGUAGE: English

L5 ANSWER 17 OF 23 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1999:21340 CAPLUS

DOCUMENT NUMBER: 130:217932

TITLE: **Gene therapy for hypertension: antisense inhibition with adeno-associated viral vector delivery targeting angiotensin II type 1-receptor messenger ribonucleic acid**

AUTHOR(S): Phillips, M. Ian

CORPORATE SOURCE: University of Florida College of Medicine, Gainesville, FL, 32610-0274, USA

SOURCE: Am. J. Cardiol. (1998), 82(10A), 60S-62S

CODEN: AJCDAG; ISSN: 0002-9149

PUBLISHER: Excerpta Medica, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Our findings suggest that prolonged redns. in blood pressure can be achieved with single doses of AAV vectors delivering antisense oligodeoxynucleotides to inhibit AT1 receptors. The findings employing antisense oligodeoxynucleotides to AT1 in spontaneously hypertensive rats recently have been extended to the 2-kidney/1-clip and cold-induced animal

models of hypertension. We have developed **rAAV-AS** vectors to deliver antisense oligodeoxynucleotides targeted to angiotensinogen and the angiotensin-converting enzyme gene. One object of further study is to identify efficient and powerful promoters to be included in DNA vectors. The results of our studies to date encourage a vision of a i-shot **gene therapy** controlling hypertension for months without side effects and thereby protecting patients from **cardiovascular** risks assocd. with high blood pressure.

REFERENCE COUNT: 8

REFERENCE(S):

- (1) Martens, J; Proc Natl Acad Sci USA 1998, V95, P2664 CAPLUS
  - (2) Phillips, M; Hypertension 1997, V29, P177 CAPLUS
  - (3) Phillips, M; Hypertension 1997, V29, P374 CAPLUS
  - (4) Phillips, M; Kidney Int 1994, V46, P1554 CAPLUS
  - (5) Tomita, N; Hypertension 1995, V26, P131 CAPLUS
- ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 18 OF 23 BIOTECHDS COPYRIGHT 2001 DERWENT INFORMATION LTD  
ACCESSION NUMBER: 1997-10823 BIOTECHDS

TITLE: Delivering gene to muscle cell or tissue using  
**recombinant adeno-associated**  
**virion;**

for use in **gene therapy** and as  
recombinant vaccine

AUTHOR: Podsakoff G M; Kessler P D; Byrne B J; Kurtzman G J  
PATENT ASSIGNEE: Avigen; Univ.Johns-Hopkins  
LOCATION: Alameda, CA, USA; Baltimore, MD, USA.  
PATENT INFO: WO 9726337 24 Jul 1997  
APPLICATION INFO: WO 1997-US895 17 Jan 1997  
PRIORITY INFO: US 1997-784757 16 Jan 1997; US 1996-588355 18 Jan 1996  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
OTHER SOURCE: WPI: 1997-385340 [35]

AN 1997-10823 BIOTECHDS

AB A new composition useful for delivering a selected gene to a muscle cell (preferably a skeletal myoblast, skeletal myocyte or **cardiomyocyte**) or tissue (e.g. derived from skeletal, smooth or cardiac muscle) contains a **recombinant adeno-associated virus** (AAV) virion containing the target gene linked to control elements. The gene preferably encodes a therapeutic protein, especially acid alpha-glucosidase (EC-3.2.1.20). The control elements consist of an inducible muscle-specific promoter sequence. Also claimed is a muscle cell or tissue transduced in vitro with the recombinant AAV virion. The virions may be used for treating type II glycogen storage disease. The target gene may also encode erythropoietin and other proteins capable of treating endocrine, metabolic, hematological and **cardiovascular** diseases including AIDS, cancer and diabetes. The virions are non-pathogenic and may be used for the delivery of antigens for immunization. Cells transduced provide sustained, high-level expression of the target gene, and the protein is secreted to provide systemic delivery. (76pp)

L5 ANSWER 19 OF 23 BIOTECHDS COPYRIGHT 2001 DERWENT INFORMATION LTD  
ACCESSION NUMBER: 1998-00955 BIOTECHDS

TITLE: **Gene transfer** into vascular cells using  
adeno-associated virus (AAV) vectors;  
**recombinant adeno-associated**  
**virus** vector-mediated beta-galactosidase reporter  
**gene transfer** to rat vascular smooth  
muscle cell and thoracic aorta for **gene**  
**therapy**

AUTHOR: Maeda Y; Ikeda U; Ogasawara Y; Urabe M; Takizawa T; Saito T;  
Colosi P; Kurtzman G; Shimada K; \*Ozawa K  
CORPORATE SOURCE: Jichi-Med.Sch.; Inst.Hematol.Tochigi; Avigen

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SOURCE: Cardiovasc.Res.; (1997) 35, 3, 514-21  
CODEN: CVREAU  
ISSN: 0008-6363

DOCUMENT TYPE: Journal

LANGUAGE: English

AN 1998-00955 BIOTECHDS

AB Beta-galactosidase (EC-3.2.1.23) reporter **gene transfer**  
into rat vascular smooth muscle cells (VSMCs) and rat thoracic aortas  
was

investigated using **recombinant adeno-associated virus** vectors. VSMCs were transduced at a  
moi of 500,000 to 10 million. Beta-galactosidase expression in VSMCs  
was

evaluated by X-Gal staining and an ELISA method. Excised rat aortas were  
incubated with medium containing the vector. Expression of  
beta-galactosidase in the aortic segments was evaluated by X-Gal  
staining. With increasing moi, up to 50% of cultured VSMCs were  
positive

by X-Gal staining and the enzyme expression increased up to 15 ng/mg  
protein. The expression gradually decreased during the culture but was  
detectable for at least 1 mth. In the ex vivo study, vectors transduced  
endothelial and adventitial cells in rat aortic segments, while no  
expression was seen in medial VSMCs. Thus, adeno-associated virus  
vectors can efficiently transduce rat VSMCs in vitro. Results suggest  
that such vectors may be used for **cardiovascular disease**  
**gene therapy**. (34 ref)

L5 ANSWER 20 OF 23 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 1997:200716 BIOSIS

DOCUMENT NUMBER: PREV199799499919

TITLE: Adeno-associated virus vectors for vascular gene  
delivery.

AUTHOR(S): Lynch, Carmel M. (1); Hara, Paul S.; Leonard, Jill C.;  
Williams, J. Koudy; Dean, Richard H.; Geary, Randolph L.  
CORPORATE SOURCE: (1) Targeted Genetics Corp., 1100 Olive Way, Suite 100,  
Seattle, WA 98101 USA

SOURCE: Circulation Research, (1997) Vol. 80, No. 4, pp. 497-505.  
ISSN: 0009-7330.

DOCUMENT TYPE: Article

LANGUAGE: English

AB A variety of delivery systems have been used to genetically modify  
vascular endothelial cells and smooth muscle cells (SMCs), but currently  
available systems suffer from either inefficient in vivo **gene**  
**transfer**, transient episomal vector expression, or significant  
immune responses and inflammation. In the present study, we evaluated an  
alternate vector system, **recombinant adeno-associated virus** (rAAV) for transduction of  
vascular cells in culture and in vivo. Primary cultures of rabbit,

monkey,  
and human SMCs; macaque and human microvascular endothelial cells; and  
human umbilical vein endothelial cells were efficiently transduced at a  
dose of 100 to 1000 DNase-resistant particles per cell. **rAAV**  
-mediated transduction of the vasculature in vivo was observed after  
intraluminal gene delivery or after intra-adventitial injection in  
carotid

arteries of atherosclerotic cynomolgus monkeys. Whether vector delivery  
was intraluminal or adventitial, transduction was observed in the  
adventitia, particularly within microvessels (vasa vasorum) but not in  
cells of the intima or media. Transduction of adventitial microvessels  
was

enhanced by balloon injury 4 days before **gene transfer**  
. This was particularly true for adventitial delivery. We have previously

shown that adventitial cell proliferation increases significantly 4 days after balloon injury (45%) in this animal model. Together, these data suggest that cell proliferation may enhance AAV transduction in vivo in the vasculature. AAV vectors exhibited a tropism in vivo for the microvascular endothelium at the doses used in the present study, which may provide the opportunity for targeting gene delivery. In summary, we have demonstrated the utility of **rAAV** vectors for ex vivo vascular cell gene delivery and present an initial experience with **rAAV** for in vivo vascular gene delivery. This alternate vector system may overcome some of the limitations hampering the development of **gene therapy** for vascular disorders.

L5 ANSWER 21 OF 23 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 1997:127708 BIOSIS

DOCUMENT NUMBER: PREV199799419521

TITLE: Prolonged reduction of high blood pressure with an in vivo,

nonpathogenic, adeno-associated viral vector delivery of AT-1-R mRNA antisense.

AUTHOR(S): Phillips, M. Ian (1); Mohuczy-Dominiak, Dagmara; Coffey, Mark; Galli, Sara M.; Kimura, Birgitta; Wu, Ping; Zelles, Tibor

CORPORATE SOURCE: (1) Dep. Physiol., Coll. Med., Univ. Florida, Gainesville, FL 32610 USA

SOURCE: Hypertension (Dallas), (1997) Vol. 29, No. 1 PART 2, pp. 374-380.

ISSN: 0194-911X.

DOCUMENT TYPE: Article

LANGUAGE: English

AB To produce a prolonged decrease in blood pressure, we have developed a nonpathogenic adeno-associated viral vector (AAV) with the antisense DNA for AT-1-R. AAV has many advantages over other viral vectors. AAV does not

stimulate inflammation or immune reaction. AAV enters nondividing cells and does not replicate. Therefore, it is an appropriate choice for **gene therapy**. Recombinant AAV was prepared with a

cassette containing a cytomegalovirus promoter and the cDNA for the AT<sub>1</sub> receptor inserted in the antisense direction. The cassette was packaged in

the virion. Stable transfection of NG108-15 cells with the pAAV-AS (plasmid AAV) antisense to AT-1-R produced a significant reduction in

AT-1 receptors. A single injection of the **rAAV-AS** (viral vector) was made in adult spontaneously hypertensive rats, either directly in the hypothalamus (1  $\mu$ L) or in the lateral ventricles (5  $\mu$ L). The result shows that there is a significant decrease of blood pressure (approx 23  $\pm$  2 mm Hg) for up to 9 weeks after injection. Control injections of mock vector produced no change in blood pressure during the same time period in

age-matched controls. In young spontaneously hypertensive rats (3 weeks), a single intracardiac injection of recombinant **rAAV-AS** reduced blood pressure and slowed the development of hypertension compared with controls (P lt .01). The results suggest that a prolonged reduction in high blood pressure can be achieved with AAV vectors delivering antisense to inhibit AT-1 receptors with a single administration.

L5 ANSWER 22 OF 23 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 1997:179938 BIOSIS

DOCUMENT NUMBER: PREV199799471651

TITLE: In vivo **gene transfer** into rat arterial

walls with novel adeno-associated virus vectors.

AUTHOR(S): Arnold, Thomas E. (1); Gnatenko, Dmitri; Bahou, Wadie F.

CORPORATE SOURCE: (1) Dep. Surg., Health Sci. Cent., T-19, 020, SUNY at Stony

Brook, Stony Brook, NY 11794-8191 USA

SOURCE: Journal of Vascular Surgery, (1997) Vol. 25, No. 2, pp.

DOCUMENT TYPE: Article  
LANGUAGE: English

AB Purpose. We studied the ability of **recombinant adeno-associated virus (rAAV)** vectors to achieve **gene transfer** in vivo to intact rat carotid arteries. Methods. Isolated segments of uninjured rat carotid arteries were incubated with (1) **rAAV** vectors that expressed a beta-galactosidase gene, (2) a related vector with no promoter, or (3) a normal saline solution. **Gene transfer** was evaluated with in situ polymerase chain reaction (PCR). Transgene expression was assessed at intervals that ranged from 24 hours to 2 months by measurement of beta-galactosidase activity and protein mass in tissue extracts with fluorometric and enzyme-linked immunosorbent assays, respectively. Dose dependence of expression was determined for virus concentrations that ranged from 5 times 10<sup>-4</sup> to 5 times 10<sup>-5</sup> infectious units (iu)/ml. Results. Light microscopic analysis of in situ PCR-stained histologic sections of transduced vessel walls showed approximately 90% of intimal and medial cell nuclei contained the beta-galactosidase gene, compared with none in control arteries. In vivo beta-galactosidase expression was (1) highest 24 hours after **gene transfer**, (2) elevated for 1 month, and (3) dose responsive. Conclusions. **rAAV** vectors can mediate focal **gene transfer** into the intact rat carotid artery with detectable levels of transgene expression for 1 month and are potentially useful agents for in vivo **gene transfer** into intact arteries.

L5 ANSWER 23 OF 23 BIOSIS COPYRIGHT 2001 BIOSIS  
ACCESSION NUMBER: 1997:127695 BIOSIS  
DOCUMENT NUMBER: PREV199799419508  
TITLE: Antisense inhibition and adeno-associated viral vector delivery for reducing hypertension.  
AUTHOR(S): Phillips, M. Ian  
CORPORATE SOURCE: Dep. Physiol., Coll. Med, Box 100274, Univ. Florida, Gainesville, FL 32610-0274 USA  
SOURCE: Hypertension (Dallas), (1997) Vol. 29, No. 1 PART 2, pp. 177-187.  
ISSN: 0194-911X.  
DOCUMENT TYPE: General Review  
LANGUAGE: English

AB Antisense oligodeoxynucleotides have been designed to inhibit the production of specific proteins. In models of hypertension, we have targeted the renin-angiotensin system at the level of synthesis (angiotensinogen) and the receptor (AT-1 receptor). The design of antisense oligonucleotides requires choosing a site to inhibit mRNA processing or translation. The strategy we use is to make three oligonucleotides of antisense sequences, upstream and downstream from the AUG site and over the AUG site. The oligonucleotides are tested in a screening test. Antisense oligonucleotides to AT-1-receptor mRNA and to angiotensinogen mRNA reduce blood pressure in spontaneously hypertensive rats when injected into the brain. They significantly reduce the concentration of the appropriate protein. The oligonucleotides are also effective when administered systemically. The decrease in blood pressure with antisense oligonucleotides delivered in blood or brain lasts 3 to 7 days. To prolong the action, direct injection of naked DNA and injection of DNA in liposome carriers have been tested. Viral vectors have been developed to deliver antisense DNA. The viral vectors available include retroviruses and adenovirus, but the adeno-associated virus (AAV) vector is the vector of choice for ultimate use in **gene therapy**. It offers safety because it is nonpathogenic, has longevity because it integrates into the genome, and has sufficient carrying capacity to carry up to 4.5 kb antisense or gene in a recombinant AAV. Using **rAAV**-antisense to AT-1 mRNA, there is efficient transfection into cells and

an



inhibition of AT-1 receptor number. In in vivo tests, **rAAV-AS** AT-1-receptor when injected into the brains of SHR reduces blood pressure for more than 2 months. In young rats (3 weeks old) **rAAV-AS** AT-1-receptor decreases blood pressure and slows the development of hypertension. While further experiments need to be done on dose-response relationships and on the cellular mechanisms of these effects, the results show the feasibility of AAV as a vector for antisense inhibition, which may ultimately be used in **gene therapy** for hypertension.